PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PV/326/PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CZ 03/00058	International filing date *(day/month/year)* 21.10.2003	Priority date *(day/month/year)* 24.10.2002
International Patent Classification (IPC) or both national classification and IPC C07C269/00		
Applicant ZENTIVA, A.S. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.04.2004	05.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bedel, C Telephone No. +49 89 2399-2506

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CZ 03/00058

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 6-14	as originally filed
3-5	received on 17.04.2004 with letter of 09.04.2004

Claims, Numbers

1-6	received on 17.04.2004 with letter of 09.04.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-6
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations

see separate sheet

The amendments filed with letter dated 9-04-04 are in conformity with the requirements of Article 34 PCT. New claim 1 is supported by a combination of original claims 1 and 3 with a passage of page 5, lines 4-8.

The application now concerns a process in 4 steps for making an optically active rivastigmine of formula II.

D1: CHEN CHUNG-PIN: TETRAHEDRON LETTERS, vol. 32, no. 49, 1991, pages 7175-7178, XP009025296
D2: US-A-5 602 176 (ENZ ALBERT) 11 February 1997 (1997-02-11)
D3: CISZEWSKA GRAZYNA: J.LABELLED COMPD.RADIOPHARM., vol. 39, no. 8, 1997, pages 651-668, XP002269029
D4: EP-A-0 193 926 (YISSUM RES DEV CO) 10 September 1986 (1986-09-10)

D1 discloses the optically active the S-m-hydroxyphenylethyldimethylamine (key intermediate in the present process).

D2 discloses the resolution of racemic rivastigmine with a tartrate salt.

D3 discloses a process for making optically active rivastigmine by asymmetric reduction to obtain the methoxy intermediate.

D4 discloses the formation of rivastigmine by reaction of carbamoyl chloride with the hydroxy intermediate (last step in present process).

D3 which is the closest prior art differs from the presently claimed process by the fact that the asymmetric carbon is introduced though an asymmetric reduction to get the S-m-methoxyphenylethyldimethylamine, which is demetylated to obtain the S-m-hydroxyphenylethyldimethylamine (see p.655, reaction scheme cpd15 -->cpd 19), while the presently claimed process makes a resolution of the racemic m-hydroxyphenylethyldimethylamine intermediate.

No other document discloses nor suggest the resolution of this intermediate to get the optically active rivastigmine.
The skilled person would have no indication in the prior art to use such a solution in order to develop an alternative process for the preparation of optically active rivastigmine.

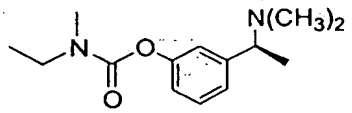
formula VII (mostly specifically N-ethyl-N-methylcarbamoyl chloride) in an about 300% excess is another drawback

Resolution in an earlier stage of the synthesis appears, at first sight, as desirable, but far from being feasible. There remains the question whether it is possible to obtain enantiomerically pure intermediates and, especially, whether these products can be used for further synthesis without being subject to racemization. The necessity of recrystallization would cast doubts on advantageousness of such procedure.

It has now turned out that optically resolving the intermediate products (i.e. performing the operation in an earlier stage of production) and performing the final step with an optically active substance, permits to obtain a very good yield of (S)-rivastigmine with retaining high analytic purity.

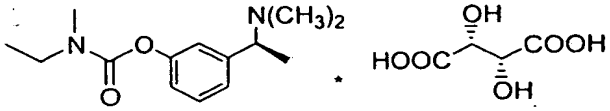
Disclosure of Invention

The present invention consists in a method of production of (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate (rivastigmine) of formula II



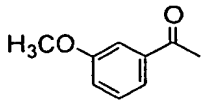
II

or of its hydrogentartrate of formula I



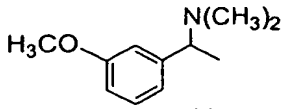
I

in which methoxyacetophenone of formula VI



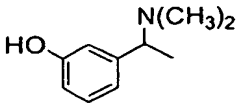
VI

is reductively aminated to the compound of formula V



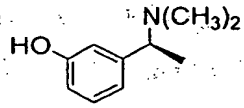
V

which is thereafter O-dealkylated to the racemic amine of formula IV



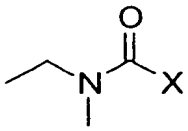
IV

which is further resolved by reacting with an optically active acid, whereafter the desired respective diastereoisomer is crystallized and finally converted into the compound of formula III



III

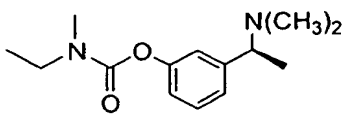
which, in turn, is reacted, optionally in the form of its alkali salt, with a compound of formula VII



VII

wherein X is a leaving group.

The resulting compound of formula II



II

is converted, by reacting with tartaric acid, into the respective salt of formula I.

Advantageously, the phenol of formula III is converted with a strong base in an inert solvent into the phenolate and it is reacted with the carbamoylhalide of formula VII.

As the strong base, hydrides of alkali metals, such as sodium hydride, or alkyl lithium compounds such as butyl lithium, can be used. The inert solvent is preferably chosen from the group of dialkyl ethers such as tetrahydrofuran or 1,2-dimethoxyethan.

The reductive amination is carried out by means of dimethylamine or its hydrochloride and a reduction agent, usually a hydride such as sodium borohydride.

The O-dealkylation agents can be selected from among strong acids, such as for example hydrobromic acid, or from among boron halides, such as boron bromide.

The racemic amine of formula IV is preferably resolved by reacting with (S)-(+)-camphor-10-sulfonic acid.

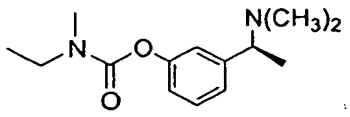
The obtained desired respective diastereoisomer can further be re-crystallized, preferably from ethylacetate, optionally in admixture with ethanol.

As is demonstrated in the examples of especially preferred embodiments, the present method makes it possible for obtaining the product of formula I in an especially high optical purity. A reproduction of the method known so far, even with recrystallization, has not resulted in obtaining such high optical purity.

It further results from comparison that use of the optically active compound of formula III results in lowering of the consumption of the expensive and carcinogenic N-ethyl-N-methylcarbamoylchloride (corresponding to general formula VII for X = Cl) by 2/3.

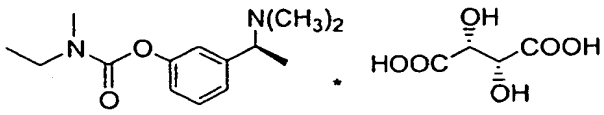
AMENDED CLAIMS

1. A method of production of (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate, i.e. rivastigmine of formula II



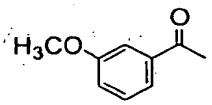
II

or of its hydrogentartrate of formula I



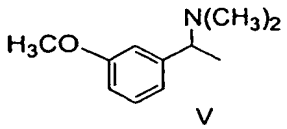
I

characterized in that methoxyacetophenone of formula VI



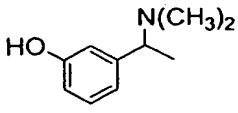
VI

is reductively aminated to the compound of formula V



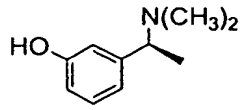
V

which is thereafter O-dealkylated to the racemic amine of formula IV



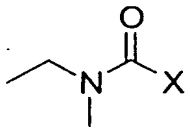
IV

which is further resolved by reacting with an optically active acid, whereafter the desired respective diastereoisomer is crystallized and finally converted into the compound of formula III



III

which, in turn, is reacted, optionally in the form of its alkali salt, with a compound of formula VII



VII

wherein X is a leaving group.

2. The method according to claim 1, *characterized in that* the racemic amine of formula IV is resolved by reacting with (S)-(+)-camphor-10-sulfonic acid.

3. The method according to claim 2, *characterized in that* the racemic amine of formula IV is resolved by reacting with 1 equivalent of (S)-(+)-camphor-10-sulfonic acid.

4. The method according to claim 2, *characterized in that* the racemic amine of formula IV is resolved by reacting with 0.6 equivalent of (S)-(+)-camphor-10-sulfonic acid.

5. The method according to any of preceding claims, *characterized in that* the obtained desired respective diastereoisomer is further re-crystallized.

6. The method according to claim 5, *characterized in that* the obtained desired respective diastereoisomer is further re-crystallized from ethylacetate, optionally in admixture with ethanol.